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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/811,192	COMMUNI ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *1-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-Final Rejection of May 19, 2006 on November 20, 2006. Claims 1-16 are withdrawn. Claim 17 is amended. Claim 18 is cancelled.

Claim 17 is under consideration. This application contains claims 1-16 drawn to an invention nonelected with traverse, March 23, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

Applicant indicates that each references which were crossed off the IDS filed September 7, 2004 have been submitted in the copending application, 10/811,198 ('198), as evidenced by the attached 1449 form in which the examiner considered all the references in an office action for '198 mailed on April 12, 2006 (Applicant's response, page 7). In response, while references of the '198 case has been considered by the examiner of that case according to that examiner's criteria, the examiner for the instant case requires that in order for the references to be considered, copies of the references must be submitted. Further, it is noted that while Applicant need not submit references if the references had been previously considered in a parent application (MPEP 609.02), '198 is not a parent of the instant case. Should Applicant wish the references be considered, they must be submitted.

Withdrawn Objection/Rejection

Specification

Applicant indicates that the specification has been amended to include SEQ ID NOs for the sequences listed on page 14 and Figure 1. Applicant has also indicated that the sequences in paper and disc format are the same. The objection with regard to the specification is withdrawn.

35 U.S.C. § 112, 2nd parag.

Applicant's arguments, see page 13 of Applicant's response, filed November 20, 2006, with respect to the rejection of claim 17 have been fully considered and are persuasive. Applicant amended the claim from "non-human mammal" to "mouse" and cancelled claim 18 and thus addressed the issue of antecedent basis and redundancy of claim 18. The rejection of claim 17 has been withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 17 remains rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

Applicant's arguments filed November 20, 2006, pages 8-10, have been fully considered but they are not persuasive.

Applicant indicates that UTP was considered as a therapeutic for cystic fibrosis, as evidenced by the University of Wisconsin's website (October 6, 2006). Further, a 1999 article by Knowles et al. teaches that extracellular UTP nucleotides are effective *in vivo* chloride secretagogues in the nasal epithelia of patients with cystic fibrosis. In response, while the Applicant provides teachings of UTP and treatment of cystic fibrosis, the teachings do not provide guidance on how to use the claimed transgenic mouse, which comprises a disruption of its P2Y4 receptor. That is, it is unclear what treatment of cystic fibrosis by UTP has to do with the claimed mouse that does not exhibit any cystic fibrosis nor is it clear how administration of the ligand UTP has any biological effect in the claimed mouse that has no P2Y4 receptor.

Applicant indicates that Merten et al., 1998 teach that cystic fibrosis results from a mutation in a gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) that lead to a defect in cAMP stimulated chloride transport (Merten et al., page 19, 1st parag.). Saleh et al., 1999 teach that human tracheal gland serous cells express CFTR and are able to respond to nucleotides through nucleotide receptor P2Y4 with an increase in chloride transport (Saleh et al., page 5077, 1st full parag.) (Applicant's response, page 9). In response, with regard to Merten et al., nothing in Merten et al. provides any teaching of P2Y4. With regard to Saleh et al. while Saleh et al. teach that human tracheal gland serous cells respond to nucleotides through P2Y4 with an increase in chloride transport, Saleh et al.'s teaching does not provide any guidance with regard to the disruption of P2Y4 and any disease or symptom of disease such that the claimed mice can be used.

Applicant indicates that teachings in the art cited by Robaye et al. (e.g. Knowles et al., 1991 and Clarke et al., 1994) are consistent with the instantly disclosed accumulation of inositol tri-phosphate upon incubation of cells expressing the polypeptide expressing the polypeptide of SEQ ID NO. 2 with UTP. Thus, the combined teachings of these references provide a reasonable correlation between the activity in question (UTP signaling mediated through cell surface receptor P2Y4 and P2Y4's physiological role in cystic fibrosis). That is, the actions of extracellular nucleotides UTP are mediated by P2Y4 receptors as disclosed in the specification and that P2Y4 receptors are a pharmacotherapeutic target for the treatment for cystic fibrosis as asserted in the specification. While Applicant indicate that Knowles et al. publication and the Clarke et al. publication indicate this relationship, this is not persuasive because while Knowles et al. and Clarke et al. generally indicate a relationship between ATP/UTP and chloride channels, neither teaches any specific role for P2Y4. Note that Robaye et al. indicate that apical chloride permeability is caused by multiple chloride channels and seems to be controlled by multiple P2Y receptors (Robaye et al., page 781, 2nd col., lines 9-11). Robaye et al.'s teaching indicates that at the time Robaye et al. disrupted the P2Y4 gene in mice, it was unclear what specific role P2Y4, compared to its other family members, was.

Applicant indicates that Robaye et al. analyzes the data obtained from the P2Y4 knockout mice and discusses it with respect to cystic fibrosis several times throughout the article. Applicant also indicates the teachings of Ghanem et al., 2005, which substantiates the potential of P2Y4 as a target for the treatment of intestinal

complications in cystic fibrosis, thus promoting the use of the P2Y4 knockout mouse as an animal model that can be used in developing cystic fibrosis therapies targeting P2Y4. In response, Robaye et al. teach P2Y4 and its role in a specific aspect of cystic fibrosis, i.e. gastrointestinal. While the specification generally indicates cystic fibrosis, the specification does not provide guidance to specifically arrive at cystic fibrosis in the gastrointestinal system. It should also be pointed out it is not entirely clear whether the phenotype exhibited by the mice correlate to a human condition as Robaye et al. also indicate that it remains to be seen whether the P2Y4 knockout mice are a model of the human condition (Robaye et al., page 782, 1st col., 2nd parag.).

As such, at the time of filing, the specification does not clearly indicate a use of the claimed mouse.

Claim 17 remains rejected.

It is noted that the rejection of claim 18 is withdrawn as the claim is cancelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 17 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's arguments filed November 20, 2006, pages 10-13, have been fully considered and they are persuasive in part.

Applicant indicates that the technology of making knockout animals, particularly mice, as required by amended claim 17 was well established at the time of the invention and is an established means of establishing animals model of disease. Applicant indicates that such unpredictability are isolated incidents and can be accommodated by methods known to one of skill in the art, such as by developing several different strains of knockout mice and/or by cross breeding (Applicant's response, pages 10-11). In response, assertion that unpredictability in arriving at phenotypes are isolated events does not overcome the fact that an artisan cannot reasonably predict that the phenotypes exhibited by the knockout mouse are related to the gene disruption and whether the phenotypes exhibited by the mouse are similar to that of a human disease or symptom of human disease. With regard to developing knockout mice in different strains and/or by cross breeding, this does not address the issue that an artisan will predictably arrive at a mouse with a readily interpretable phenotype. As taught by Doetschmann (previously cited, see page 140, 2nd col., under "Effects of genetic background on phenotypic variation"), an artisan cannot reasonably predict what effects genetic backgrounds will have on the mice following gene disruption; subsequently, it is unclear what mouse strains are ideal to use such that an artisan readily arrives at a mouse with a phenotype that is related to the disrupted gene. As such, generally

indicating that transgenic mice can be crossbred or be made in any genetic background does not enable an artisan to arrive at a mouse that can be readily used. Thus, the rejection as it applies to the predictability in arriving at transgenic mice remains.

Applicant indicates that P2Y4 belongs to the family of G-coupled protein receptors, of which knockout animals have been successfully produced. In response, while the P2Y4 knockout mouse appears to produce a mouse with a gastrointestinal phenotype (Robaye et al. publication), which may be similar to a gastrointestinal disorder in cystic fibrosis patients, the production of the mouse by Royabe et al. was not contemplated in the specification, as the specification generally contemplates P2Y4 to generally have a role in cystic fibrosis (specification, page 8, lines 4-5), but does not indicate that the knockout mouse would have a specific phenotype. Because the specification does not provide guidance for arriving at a transgenic P2Y4 knockout mouse, an artisan is not enabled to arrive at the claimed invention. Thus, the rejection as it applies to the predictability in arriving at transgenic mice remains.

Applicant indicates that the Office Action states that the use of the claimed knockout mouse as a model of disease or use in an application for human therapy is not clear at the time of filing. Applicant contends that application of these mice for human therapy is not required to be explicit, as evidenced by In re Brana 51F.3d at 1567, 34 USPQ2d at 1442 (Applicant's response, page 11). In response, it is not entirely clear why Applicant provided the excerpt of Brana because nothing in the excerpt discusses transgenic mice and whether or not they require being models of disease. While it certainly is not a requirement that transgenic mice are models of disease, nothing in the

specification provides guidance of other uses of the claimed mice. That is, an art accepted use of transgenic mice is that they are models of disease; however, failing that and not being told of other uses, the use of the claimed mice is not readily apparent. Thus, the rejection as it applies to what use the claimed mouse has remains.

With regard to the issue that the specification does not provide guidance for an artisan to practice the full scope of non-human mammals, Applicant has amended the claim to "mouse" (Applicant's response, page 12). The rejection as it applies to this issue is withdrawn.

Thus, claim 17 remains rejected.

The rejection of claim 18 is withdrawn as claim 18 is cancelled.

Priority

Applicant indicates that the specification and the art provide guidance for an artisan to arrive that the claimed invention (Applicant's response, page 13). In response, this has not been found persuasive because neither the instant application nor applications to which priority is claimed provide an enabling disclosure. Nothing in the specification or art provides guidance that an artisan would have arrived at the claimed mice, and nothing in the specification indicates that an artisan would have arrived at the mice described by Robaye et al. Given the unpredictability in the art at arriving at transgenic mice and given that there are no working examples in the specification, an artisan would not have reasonably predicted in arriving at any mouse

with any particular phenotype. As such, the priority of the application is March 26, 2004.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 17 remains rejected under 35 U.S.C. 102(a) as being anticipated by Robaye et al., 2003, Molecular Pharmacology, 63: 777-783 (previously cited).

Applicant's arguments filed November 20, 2006, pages 13-14, have been fully considered but they are not persuasive.

Applicant indicates that Robaye et al. is not prior art given that Applicant claims priority and is entitled to the benefit of prior-filed Applications. As indicated above in "Priority," the prior-filed Applications do not provide support for an artisan to arrive at the claimed invention, and thus, the rejection as it applies to claim 17 remains.

The rejection of claim 18 is withdrawn as claim 18 is cancelled.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER